PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GOUDREAU GAGE DUBUC
Stock Exchange Tower
Attn. Dubuc, J.
800 Place Victoria, Suite 3400
P.O. Box 242
Montréal, Québec H4Z 1E9
CANADA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference CG/11168.242	Date of mailing *(day/month/year)* 04/02/2005 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/CA2004/001009	International filing date *(day/month/year)* 14/07/2004
Applicant MCGILL UNIVERSITY	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41–22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Joannes Vergoosen

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
CG/11168.242		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA2004/001009	14/07/2004	14/07/2003
Applicant		
MCGILL UNIVERSITY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/001009

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] in written format

   [X] in computer readable form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [ ] filed together with the international application in computer readable form

   [X] furnished subsequently to this Authority for the purpose of search

2. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/001009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N7/00 C12N5/06 C12Q1/70 A61K39/29 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUELLER HUBERT M ET AL: "Peripheral blood leukocytes serve as a possible extrahepatic site for hepatitis C virus replication" JOURNAL OF GENERAL VIROLOGY, vol. 74, no. 4, 1993, pages 669-676, XP009022599 ISSN: 0022-1317 page 675	1-7,13
A	the whole document	8-12, 14-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2005	04/02/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schulz, R

4

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MUELLER H M ET AL: "B-lymphocytes are predominantly involved in viral propagation of hepatitis C virus (HCV)" ARCHIVES OF VIROLOGY, NEW YORK, NY, US, no. SUPPL 9, 1994, pages 307-316, XP009022615 ISSN: 0304-8608 the whole document	1-21
A	LASKUS TOMASZ ET AL: "The presence of active hepatitis C virus replication in lymphoid tissue in patients coinfected with human immunodeficiency virus type 1" JOURNAL OF INFECTIOUS DISEASES, vol. 178, no. 4, October 1998 (1998-10), pages 1189-1192, XP008041838 ISSN: 0022-1899 page 1191 the whole document	1-21
A	CRIBIER BERNARD ET AL: "In vitro infection of peripheral blood mononuclear cells by hepatitis C virus" JOURNAL OF GENERAL VIROLOGY, vol. 76, no. 10, 1995, pages 2485-2491, XP009022598 ISSN: 0022-1317 the whole document	1-21
A	US 5 716 845 A (SUGDEN ET AL) 10 February 1998 (1998-02-10) the whole document	1-21
P,X	WO 2004/013318 A (UNIV MCGILL ; SONENBERG NAHUM (CA); LOPEZ-LASTRA MARCELO (CA)) 12 February 2004 (2004-02-12) the whole document	1-21
T	LIU C: "624 Culture and immortalization of hepatitis C viral positive human hepatocytes" HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 38, 2003, page 462, XP004623839 ISSN: 0270-9139 the whole document	1-21
T	CABRERA R ET AL: "626 CD4<+> CD25<+> regulatory T lymphocytes respond directly to HCV antigens via cytokine release and suppress HCV-specific T cell responses" HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 38, 2003, pages 462-463, XP004623841 ISSN: 0270-9139	1-21

4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

Present claims 14 - 17 relate to an extremely large number of possible in vitro replication systems, comprising any EBV-transformed B cell capable of replicating complete and infectious HCV as well as any second cell population having HCV tropism and in which robust HCV replication was possible; present claims 18 - 19 further refer to an assay of screening a test agent making use of such a replication system testig any biological function of the HCV produced from the cell line or cell population and present claims 20 - 21 relate to a method for identifying a compound with anti-HCV activity from a library of compounds based on said screening assay. Support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the compounds and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to Example XXI. disclosing a co-culture system comprising an EBV-immortalized cell line derived from an HCV positive donor and PBLs from an HCV negative donor (Fig. 43).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/001009

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ernational Application No
PCT/CA2004/001009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5716845 A	10-02-1998	JP 8168382 A	02-07-1996
WO 2004013318 A	12-02-2004	WO 2004013318 A1	12-02-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

Due : 05 , 14 , 05
mm dd yy

INSCRIPTION

PCT

Goudreau Gage Dubuc
PROPRIÉTÉ INTELLECTUELLE

M.G.
TRANSMISSION

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/001009	14.07.2004	06.02.2004

International Patent Classification (IPC) or both national classification and IPC
C12N7/00, C12N5/06, C12Q1/70, A61K39/29, G01N33/50

Applicant
MCGILL UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Schulz, R Telephone No. +31 70 340-4381

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001009

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-7, 13
Inventive step (IS)	Yes:	Claims	14-21
	No:	Claims	8-12
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: Müller, H. M. et al. (1993) Peripheral blood leukocytes serve as a possible extrahepatic site for hepatitis C virus replication. J. General Virol. 74, 669 - 676.

D2: Laskus, T. et al. (1998) The presence of active hepatitis C virus replication in lymphoid tissue in patients coinfected with Human Immunodeficiency Virus Type 1. J. Infect. Diseases 178, 1189 - 1192.

D3: Cribier, B. et al. (1995) In vitro infection of peripheral blood mononuclear cells by hepatitis C virus. J. General Virol. 76,

V.2 **NOVELTY** (Art. 33(1)(2) PCT)

V.2.1 The present application does not meet the criteria of Art. 33(1) PCT, because the subject-matter of claims 13 and 1 - 7 and is not new in the sense of Art. 33(2) PCT: document D1 already discloses Epstein-Barr virus transformed B lymphocytes derived from an HCV-infected patient showing specific amplification of HCV RNA (p. 675, right hand-side column, 3rd para).

V.2.2 Subject-matter of claims 14 - 21 are considered as novel over the state of the art and thus to meet the requirements of Art. 33(2) PCT.

V.3 **INVENTIVE STEP** (Art. 33(1)(3) PCT)

V.3.1 The present application does not meet the criteria of Art. 33(1) PCT, because the subject-matter of claims 8 - 12 does not involve an inventive step in the sense of Art. 33(3) PCT.

V.3.2 The document D1 is regarded as being the closest prior art to the subject-matter

of claims 8 - 12 and discloses Epstein-Barr virus transformed B lymphocytes derived from an HCV-infected patient showing specific amplification of HCV RNA (p. 675, right hand-side column, 3rd para).

V.3.3 The subject-matter of said dependent claims differs in that the method referred to in claim 1 is further defined, i.e. the PBL fraction derived from an HCV positive patient and certain aspects with regard to the culturing conditions for the cell line claimed.

V.3.4 However, in view of the state of the art, dependent claims 8 - 12 are considered as not containing any features which, in combination with the features of any claim to which they refer, and as not to meet the requirements of the PCT in respect of inventive step.
D2 discloses a study aimed to resolved the issue of HCV lymphotropism by searching for the presence of HCV RNA negative strand in PBMC and lymph nodes of HIV infected drug addicts which had not yet received any antiviral therapy. The analysis revealed the presence of active HCV replication in PBMC and lymph nodes of these subjects. The authors discuss why HCV replication seemed more efficient in cells from these donors and assume that a weakened immune pressure against infecting HCV leads to development/persistence of HCV variants capable of replication in PBMC (p. 1191).
Based on D2's disclosure, the skilled person is considered as to regard PBMC or PBL from the group of donors disclosed in D2 as a straightforward and to combine with his/her general technical knowledge in order to achieve a higher efficiency of HCV replication.

V.3.5 The document D3 is regarded as being the closest prior art to the subject-matter of claim 14 and discloses a study of PBMC susceptibility to HCV. To that aim, cells from healthy donors were incubated with HCV positive sera (p. 2485 - 2487). Infection of cultured PBMC was observed but the replication level in that system was very low (p. 2490).

V.3.6 The subject-matter of claim 14 differs in that it refers to a cell-based *in vitro* replication system based on co-culturing an EBV transformed B-cell replicating

complete and infectious HCV and another cell population having HCV tropism.

V.3.7 The problem to be solved by the present invention may therefore be regarded as the provision of an improved HCV *in vitro* replication system.

V.3.8 The solution proposed in claims 14 - 17 of the present application is considered as involving an inventive step in the sense of Art. 33(3) PCT for the following reasons: although it is known in the art that cultured PBMC which are an extrahepatic site for HCV replication (D1, D2) can be HCV infected with sera from positive donors and moreover an EBV transformed B-cell capable of replicating complete and infectious HCV has been already been disclosed (D1), none of these documents neither suggested nor provided an incentive to combine those teachings in order to establish an HCV *in vitro* replication system referred to in said claims.

V.3.9 In line with the above, subject-matter of claims 18 - 21 is considered as comprising an inventive step in the sense of Art. 33(3) PCT.

However, at present claims 14 - 21 cannot be considered as to meet the requirements of the PCT due to certain deficiencies mentioned below (VIII.1).

Re Item VIII (clarity)
Certain observations on the international application

VIII.1 **CLARITY** AND **SUPPORT** (Art. 5 PCT, Art. 6 PCT)

VIII.1.1 Present claims 14 - 17 relate to an extremely large number of possible *in vitro* replication systems, comprising any EBV-transformed B cell capable of replicating complete and infectious HCV as well as any second cell population having HCV tropism and in which robust HCV replication was possible. Said claims do not meet the requirements of Art. 6 PCT in that the matter for which protection is sought is not clearly defined by referring to technical features. Moreover, they cannot be considered as being supported over the whole breadth of their scope. In addition, said claims attempt to define their subject-matter in terms of the result to be achieved, i.e. "... so that under appropriate culture conditions said second cell

population can become infected by said infectious HCV produced by said EBV-transformed B-cell" which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

The same reasoning applies to the subject-matter of claims 18 - 19 which refers to an assay of screening for a test agent making use of the above replication system and testing a not further defined biological function of the HCV produced from the cell line or cell population and to the subject-matter of present claims 20 - 21 relating to a method for identifying a compound with anti-HCV activity from a library of compounds based on said screening assay.

VIII.1.2 Support within the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT for claims 14 - 21 can be found in the description (e.g. Example XXI., Fig. 43), however, for only a very small proportion of the compounds and methods claimed. Therefore, the claims are considered as lacking support in the sense of Art. 6 PCT and the application as lacking disclosure in the sense of Art. 5 PCT.